Low-Barrier Hydrogen Bonds: *Ab Initio* and DFT Investigation

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ABSTRACT: High-level *ab initio* and DFT molecular orbital calculations have been used to investigate the physical properties of a model low-barrier hydrogen bond (LBHB) system: formic acid–formate anion. In the gas phase, it is found that the hydrogen bond formed is extraordinarily short and strong [ca. 27 kcal/mol at B3LYP/6-31 + + G(d, p)], with a calculated enthalpy of activation for proton transfer from donor to acceptor that is less than the zero-point vibrational energy available to the system. Several perturbations to this system were studied. Forcing a mismatch of pK_as between donor and acceptor, via the use of substituents, causes the strength of the hydrogen bond to decrease. Microsolvation of the hydrogen-bonded complex does not affect the strength of the low-barrier hydrogen bond very much. Small variations in the structure of the LBHB results in a decrease in hydrogen-bond strength. Increasing the effective polarity of the cavity surrounding the LBHB was found to have a significant impact on the strength of the hydrogen bond. Implications for enzyme catalysis are discussed. © 1998 John Wiley & Sons, Inc. J Comput Chem 19: 1345–1352, 1998

Keywords: *ab initio* calculations; low-barrier hydrogen bonds; enzyme catalysis; density functional calculations; hydrogen bonding

Introduction

There has been a great deal of interest in ''short–strong'' or ''low-barrier'' hydrogen bonds (LBHBs) in recent years.[1–16] Most of this interest has stemmed from the suggestion by Cleland, Kreevoy, Gerlt, and Gassman that the formation of a single short–strong, or low-barrier, hydrogen bond during an enzyme catalytic event can provide enough stabilization energy to account for the resulting rate enhancements typically seen in enzymatic reactions.[4–6] Briefly, their proposal involves a mechanism whereby an enzyme-bound intermediate, or transition state, is stabilized by the formation of a single LBHB. They hypothesize

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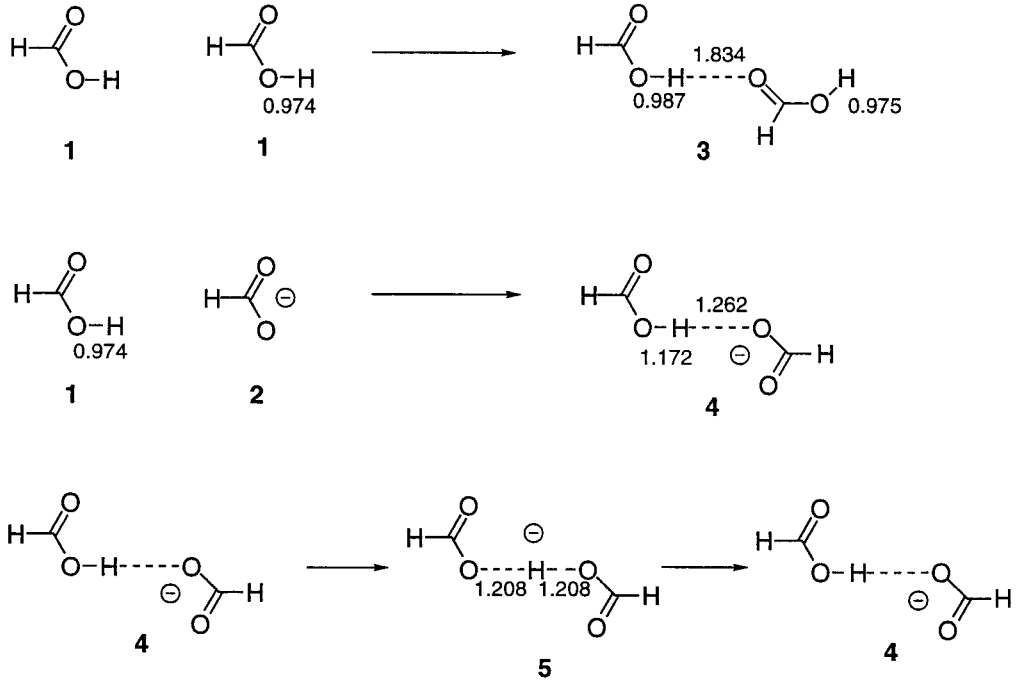
that such a bond, if formed, could provide 10–15 kcal/mol of stabilization energy to the enzyme complex. This would then be enough to rationalize the rate accelerations observed during many enzyme-catalyzed reactions. This hypothesis has certainly not been without criticism. The most ardent opponents of the low-barrier hydrogen bond facilitated enzyme mechanism have been Guthrie and Kluger,[7a] Guthrie,[7b] Warshel et al.,[8] Scheiner and Kar,[9] and Perrin,[10a] although there have certainly been others.[2, 3–12]

All of the available experimental and theoretical evidence to date suggests that the formation of LBHBs is dependent on several conditions being met: (1) the proton donor and proton acceptor must have identical, or nearly identical, pK_as; (2) the proton donor must be a fairly strong acid; (3) almost all LBHBs are charged systems; and (4) absence of a hydrogen-bonding, or polar solvent. Most opponents of the LBHB-facilitated enzyme mechanism use this last criterion to stress their point. That is, if a LBHB cannot exist in solution, surely it cannot exist in an enzyme active site. Of course, that argument assumes that bulk solution and enzyme active sites are similar. That may or may not be true.

The simplest catalytic unit available to most enzymes is the carboxylate, present in all natural amino acids, and as a side chain in aspartic (Asp) and glutamic (Glu) acids. The fundamental importance of the Asp and Glu residues for catalysis has long been identified, particularly in enzymes such as the proteases and the enolases. It is the precise role, however, that the Asp or Glu plays in such catalysis that is being debated.[11] We have chosen to study the simplest Asp and Glu models: the interactions between two formic acids, and between a formic acid and a formate anion (Scheme I). It is well known that the strongest hydrogen bonds are formed when the proton donor and the proton acceptor have matching pK_as.[13] Thus, the choice of studying the interaction between formic acid and formate anion should represent the best possible situation for the formation of a LBHB.

Our research[17] has focused on the detailed characterization of low-barrier, and other short–strong, hydrogen bonds that are postulated to be important during enzyme catalysis, using modern *ab initio* and density functional theory calculations. We first study such systems under ''ideal'' conditions; that is, perfectly matching pK_as (gas phase acidities) between the donor and acceptor moieties; fairly strong acids; optimum geometries; and no interfering solvent molecules. We then perturb these ideal conditions to see what effect that would have on the resulting hydrogen bonds, and infer what this might mean for the corresponding enzyme processes. It is not the purpose of this study



SCHEME I. Compound numbers and selected optimized geometrical parameters [B3LYPM-31++G(d, p)] for **1**–**5**.

to simulate, or calculate, free energies of solvation of individual ions,[18] or the hydrogen-bonded complexes. The methods employed herein are not suitable for such studies. We are primarily interested in what affects various environmental factors (including the reaction with a *limited* number of solvent molecules) have on the symmetries and stabilities of LBHBs.

Methodology

All calculations were performed using the Gaussian-94 suite of programs.[19] Standard split-valence basis sets[20] of 6-31G quality were used as supplied in Gaussian-94, with added diffuse and polarization functions to make the basis sets more flexible. Specifically, we have used the 6-31 + G(d), 6-31 + G(d, p), and the 6-31 + + G(d, p) basis sets routinely in this work.

Calculations have been performed at various levels of theory, including Hartree–Fock, Møller–Plesset (MP2), and density functional.[21] We have used the BLYP and B3LYP functionals in this work. These functionals are described elsewhere.[22–25]

All geometries were completely optimized, with the exception that the central hydrogen bond was forced to be linear, to avoid situations where multiple hydrogen bonds might form. This constraint was necessary to avoid the energetically more favorable, but theoretically less interesting, hydrogen-bonded dimers from forming. That is, because the two constituents of the LBHB in an actual enzyme active site are surely unable to form a true dimer, due to flexibility constraints of the enzyme, we have chosen to study our model system in a likewise ''extended'' conformation.

Results and Discussion

''GAS-PHASE'' STUDIES

Structures and energies for compounds **1**–**5** were calculated at the HF, MP2, B3LYP, and BLYP levels of theory, using the 6-31 + + G(d, p) basis set. Hydrogen bond (E_{HB}) energies are determined as the difference in total calculated energy between the corresponding complex and the constituent monomers. The activation energy (E_A) for proton transfer is calculated as the energy difference of compounds **4** and **5**. Full tables of calculated energies and geometries of compounds **1**–**11** can be found in the Wiley Electronic Database. Selected optimized bond lengths at the B3LYP/6-31 + + G(d, p) level of theory are shown in Schemes I and II.

As Table I shows, the hydrogen-bond energy between formic acid and formate anion is very large. These calculations predict that E_{HB} is approximately 27 kcal/mol. HF calculations predict a slightly weaker interaction (22 kcal/mol). The correlated calculations find two discrete stationary points corresponding to the symmetrically hydrogen bonded structure (**5**) and the asymmetrically hydrogen-bonded system (**4**). At each level of theory the asymmetrical structure, which is a true minimum, is slightly lower in energy than the symmetric structure, which is a transition state, resulting in very small calculated energy barriers for proton transfer (Table I). Inclusion of zero-point vibrational energy causes the hydrogen to resonate above the intrinsic barrier for proton transfer. On the other hand, the calculated interaction energy between a formic acid molecule and another formic acid molecule (**3**) is only ca. 5–6 kcal/mol. This is

TABLE I.
Calculated Hydrogen Bond (E_{HB}) and Activation Energies (E_A) for Proton Transfer Using 6-31 + + G(d, p) Basis Set (kcal/mol).

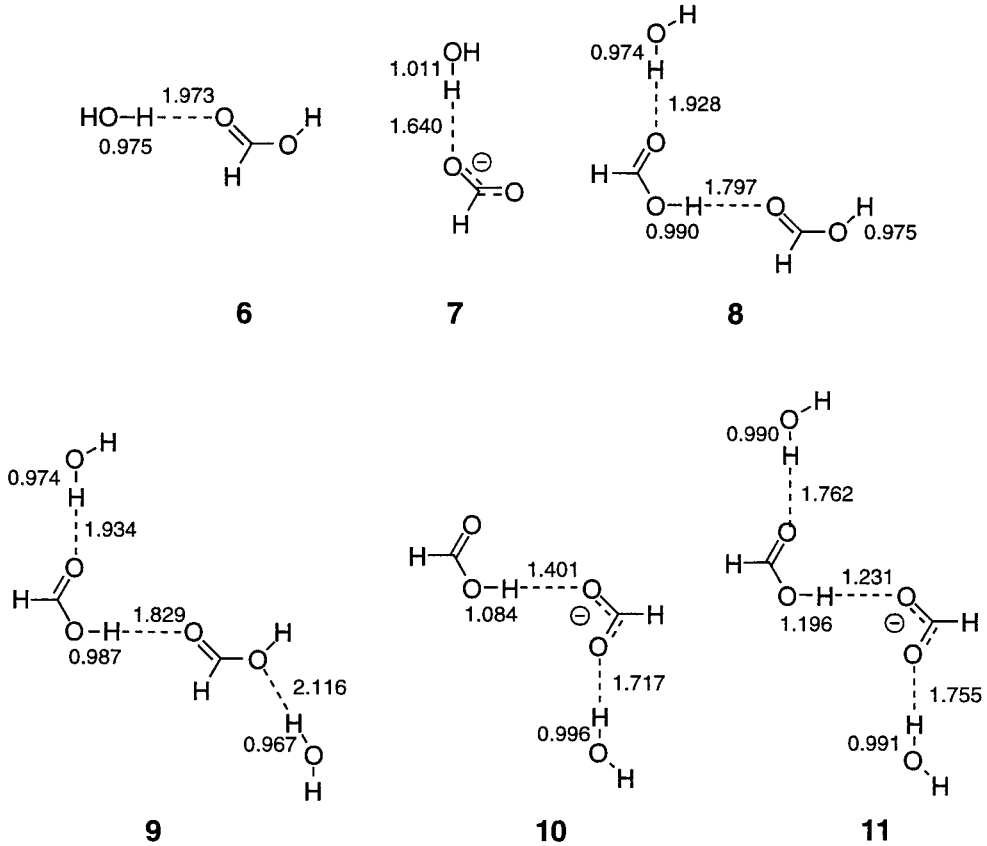
	HF	MP2	BLYP	B3LYP
Formic acid–formic acid (**3**)				
E_{HB}	4.7	6.1	4.7	5.4
Formic acid–formate anion (**4**)				
E_{HB}	22.2	26.9	26.8	27.2
E_A	1.40	0.01	0.02	0.00
E_A + ZPVE	−0.90	−0.02	−0.01	−0.27

dramatically weaker than the interaction between formic acid and formate anion, and underscores the importance of charge in generating a short, strong hydrogen bond.

MICROSOLVATION STUDIES

To determine the effect of 'microsolvation' on the strength of low-barrier hydrogen bonds we reoptimized the structures of **1**–**4** in the presence of one or two water molecules, using the 6-31++G(d, p) basis set, and HF, MP2, B3LYP, and BLYP levels of theory. This resulted in several new complexes as shown below in Scheme II.

Table II shows the results of our microsolvation studies on the formic acid–formate anion system. The hydrogen bond energy (E_{HB}) was calculated as the difference in total energy between the microhydrated complex and the corresponding microhydrated monomer(s). For instance, the E_{HB} for complex **8** is calculated as the difference in energy between monomer **1** and the microhydrated monomer, **6**. Analogous comparisons led to the calculated E_{HB}s for complexes **9**, **10**, and **11**. The data in Table II show that the introduction of one water molecule hydrogen bonded to the most basic oxygen of the anionic complex **4** weakens the corresponding central hydrogen bond by approximately 3 kcal/mol. This is readily understandable because the introduction of the water molecule disrupts the perfect balance of pK_as between the hydrogen-bond donor and acceptor—that is, the donor and acceptor are no longer perfectly matched, because one is hydrogen bonded to an external water molecule, whereas the other is not. The surprising result is that this lowering of the E_{HB} is not more severe. Introduction of a second water molecule (symmetrically placed) rebalances the match in pK_as (gas-phase acidities) between donor and acceptor, and the corresponding E_{HB} increases again. Interestingly, the calculated E_{HB} for **11**, which is microsolvated by two water molecules, is several kilocalories per mole *higher* than the E_{HB} for the parent complex **4** (without



6 **7** **8**

9 **10** **11**

SCHEME II. Compound numbers and selected optimized geometrical parameters [B3LYP6-31++G(d, p)] for **6**–**11**.

TABLE II.
Calculated Hydrogen-Bond (E_{HB}) Energies for Microsolvated Formic Acid–Formate Anion Complexes Using 6-31++G(d, p) Basis Set (kcal/mol).

	HF	MP2	BLYP	B3LYP
Formic acid–formic acid–H_2O (**8**)				
E_{HB}	5.5	7.0	5.8	6.4
Formic acid–formate anion–H_2O (**10**)				
E_{HB}	20.1	23.4	22.9	23.4
H_2O–formic acid–formic acid–H_2O (**9**)				
E_{HB}	4.7	6.1	4.6	5.5
H_2O–formic acid–formate–H_2O (**11**)				
E_{HB}	24.7	29.5	29.6	29.9

any water molecules). This suggests that small amounts of water, symmetrically placed, will actually increase the strength of a LBHB. This type of hydrogen bond cooperativity has been proposed (and observed) previously.[28] However, because it is well known that LBHBs cannot survive in polar-protic media, it is certainly surprising, and noteworthy, that a small amount of external hydrogen bonding solvent does not disrupt the LBHB, but in fact enhances it.

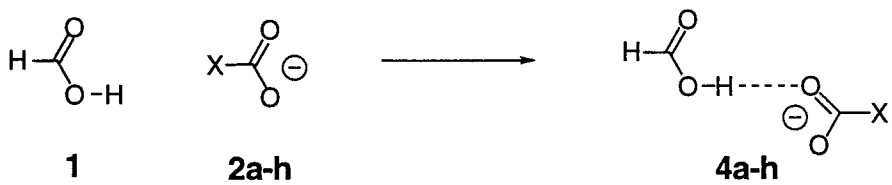
pK_a MISMATCH

The consequence of causing a pK_a (gas-phase acidity) mismatch between the hydrogen-bond donor and the hydrogen-bond acceptor was studied by introducing a substituent at the "X" position of formate, and studying the corresponding interaction energy (E_{HB}) as a function of substituent (Scheme III).
where **a**: X = H; **b**: X = CH_3; **c**: X = CH_2F; **d**: X = CHF_2; **e**: X = CF_3; **f**: X = F; **g**: X = CN; **h**: X = SH.

Fully optimized structures for **2a**–**h** and **4a**–**h** were studied using the 6-31+G(d, p) basis set and HF, MP2, B3LYP, and BLYP levels of theory. Table III contains the results of our substituent effect study. The calculated hydrogen bond energies are determined at the total energy of formic acid (**1**) plus the total energy of a substituted formate anion (**2a**–**h**) minus the total calculated energy of the corresponding complex (**4a**–**h**). The results clearly show that the introduction of any substituent leads to a decrease in the calculated E_{HB}. This is consistent with the notion that E_{HB} will be maximum when the pK_a (gas-phase acidity) of the donor and acceptor are identical, and lowered whenever they are different. The differences in calculated E_{HB} correlates roughly with the calculated differences in proton affinities for the substituted formate anions. It is clear that any imbalance of the pK_as (gas-phase acidities) causes a decrease in the calculated E_{HB} for these LBHBs. The largest effect here is between the parent complex (**4a**) and the CN-substituted complex (**4g**). The introduction of the cyano substituent causes an approximately 7-kcal/mol decrease in the calculated E_{HB}. The difference in calculated proton affinities for **2a** and **2g** is 16 kcal/mol. This corresponds to a pK_a difference of ca. 4 units in solution (at room temperature). Thus, we would predict that a pK_a mismatch in an enzyme active site of 1 pK_a unit will cause a fairly moderate (2 kcal/mol) decrease in the strength of the corresponding hydrogen bond formed.

NONIDEAL GEOMETRIES

All of our studies thus far have assumed that each LBHB system could adopt its ideal, or perfect, geometry (within the constraint of having a



SCHEME III. Compound numbering scheme used for substituent effect study.

TABLE III.
Calculated Hydrogen Bond Energies (kcal/mol) for Substituted Formic Acid–Formate Anion Complexes Using 6-31+G(d, p) Basis Set.

Substituent X	Hydrogen–bond energy (kcal/mol)			
	HF	MP2	BLYP	B3LYP
H	22.2	26.9	26.8	27.2
CH_3	23.0	—	—	—
CH_2F	21.2	25.1	24.4	26.4
CHF_2	19.4	23.1	22.6	25.2
CF_3	17.8	21.2	20.4	21.1
F	18.2	20.7	19.9	21.1
CN	16.3	20.2	19.2	19.7
SH	17.3	21.0	18.4	19.7

linear H bond). However, it is certainly possible that in many ''real'' systems, such as enzyme active sites, the ideal geometry will not be attainable, due to other constraints placed on the system. We have thus investigated in detail the energetic consequences on E_{HB} of displacing the formic acid–formate anion (**4**) system from its equilibrium geometry. The calculations were performed at the HF, MP2, and B3LYP levels of theory using the 6-31+G(d, p) basis set. These calculations take the infinitely separated monomers (**1**, **2**) as the zero energy E_{HB}, which we approximate by a O—O separation of 50 Å. The O—O separation is then reduced systematically and the energy of each new complex is recalculated after the geometry was allowed to completely relax and reoptimize (except for the O—O distance, of course). The results show that a variation in the O—O distance from the optimum value (ca. 2.43 Å, B3LYP) by as little as 0.5 Å (to 2.9 Å) results in a lowering of E_{HB} by approximately 6 kcal/mol (B3LYP). A 1.0-Å change in the O—O distance causes a decrease in E_{HB} of over 13 kcal/mol (B3LYP). Thus, we conclude that the strength of a LBHB is quite sensitive to the actual geometry of the hydrogen bond. If macro effects prevent the LBHB from forming completely, as is certainly possible in enzyme active sites, these calculations suggest that the resulting hydrogen bond would be significantly weakened.

CAVITY POLARITY EFFECTS

To ascertain the consequences of increasing the polarity of the ''cavity'' within which the LBHB is formed, we have performed self-consistent reaction field (SCRF) simulations employing various dielectric continuums. The SCIPCM method of Tomasi and coworkers,[27] as implemented in Gaussian-94, was used for these simulations. Single-point energy calculations using the 6-31++G(d, p) basis set were run for each of **1**–**5** at each level of theory previously employed in the gas-phase simulations for solvent dielectric constant values (ε) of 1.0, 2.3, 6.0, 15.0, 23.0, 35.0, 47.0, and 79.0. The corresponding E_{HB} and E_A values were then recomputed using the new energy values. Results of these simulations are given in Table IV, and pre-

TABLE IV.
Calculated Hydrogen Bond (E_{HB}, kcal/mol) and Activation (E_A, kcal/mol) Energies for Formic Acid–Formic Acid Complex (3) and Formic Acid–Formate Anion Complex (4) Using HF/6-31++G(d, p)-Optimized Geometries.

	Dielectric constant (ε)							
	1.0	2.3	6.0	15.0	23.0	35.0	47.0	79.0
HF[a]								
E_{HB} (**3**)	4.7	3.8	3.1	2.8	2.7	2.6	2.6	2.6
E_{HB} (**4**)	22.2	13.7	9.6	8.0	7.6	7.4	7.3	7.2
E_A	1.4	1.8	2.2	2.4	2.3	2.4	2.4	2.4
BLYP[b]								
E_{HB} (**3**)	4.3	4.1	3.7	3.5	3.4	3.4	3.4	3.3
E_{HB} (**4**)	25.0	17.7	13.7	12.5	12.3	12.1	11.9	11.9
E_A	−1.6	−1.1	−1.0	−0.3	−0.1	−0.3	−0.6	−0.3
B3LYP[c]								
E_{HB} (**3**)	5.0	4.6	4.1	3.8	3.8	3.7	3.7	3.7
E_{HB} (**4**)	25.9	18.3	14.4	12.7	12.5	12.0	12.0	12.0
E_A	−1.3	−1.2	0.0	−0.2	0.1	−0.8	−0.5	1.1

[a] HF/6-31++G(d, p)//HF/6-31++G(d, p).
[b] BLYP/6-31++G(d, p)//HF/6-31++G(d, p).
[c] B3LYP/6-31++G(d, p)//HF/6-31++G(d, p).

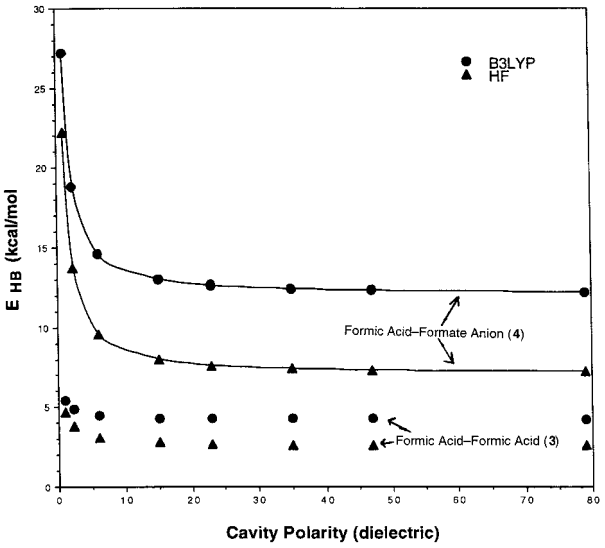


FIGURE 1. Calculated hydrogen bond (E_{HB}) energy (kcal/mol) in the formic acid–formic anion (**4**) and formic acid–formic acid (**3**) systems as a function of the dielectric constant of the medium (ε), for HF and B3LYP levels of theory, with the 6-31++G(d, p) basis set.

sented graphically in Figure 1. From Figure 1 we can see that there is a significant decrease in the calculated E_{HB} as the dielectric constant of the surrounding medium is increased for the formic acid–formate anion system (**4**), but very little effect on the formic acid–formic acid system (**3**). Of equal significance, however, is the leveling off effect in these plots—that is, although there is a rapid, sudden, and dramatic decrease in E_{HB} of **4** as the dielectric constant is increased, this effect levels off rather quickly, and by the time a dielectric constant of 15 is reached, there is little or no further effect of increasing the dielectric constant of the surrounding medium. Thus, the calculated E_{HB} for a model LBHB does not approach zero as the dielectric constant is increased, but rather results in a calculated E_{HB} of approximately 12 kcal/mol (at this level of theory). Similarly, there is a small dielectric effect on the neutral hydrogen bond of **3**, leveling off at approximately 3 kcal/mol. This would suggest that, even in a very polar enzyme active site, an ionic LBHB could provide 9 kcal/mol more stabilization energy than a traditional neutral hydrogen bond.

Conclusions

High-level *ab initio* and DFT calculations have been used to study the short, strong hydrogen bond formed between formic acid and formate anion (**4**). In the gas phase, this system forms a very strong, low-barrier hydrogen bond. The calculated E_{HB} for this system is ca. 27 kcal/mol. Thus, these results suggest that the LBHB-facilitated mechanism, as suggested by Gerlt, Gassman, Cleland, and Kreevoy,[4–6] for enzyme catalysis, *is* plausible in the gas phase. Because enzymes do not exist in the gas phase, we have investigated many perturbations to these systems to observe what happens to the resulting strength of the hydrogen bond. Cavity polarity simulations were found to have the largest effect on calculated E_{HB} values. The short–strong HB in **4** was reduced from 27 kcal/mol in a medium of dielectric 1.0, to 12 kcal/mol in a cavity of dielectric 20 or greater. This reduced the catalytic advantage of forming a LBHB in an enzyme active site to only 9 kcal/mol versus a traditional neutral hydrogen bond. Microsolvation effects were studied via the use of specific water molecules. It was concluded that the resulting E_{HB} for the asymmetrically hydrated complex of formic acid–formate anion (**10**) was about 3 kcal/mol weaker than the corresponding non-microhydrated system (**4**). On the other hand, symmetrically placed water molecules actually led to an increase in the calculated E_{HB} for this system. This strongly suggests that the presence of a small amount of water, or other hydrogen bonding solvent, within the enzyme active site, is insufficient to break up a LBHB, and, in fact we predict that such an environment would most likely increase the strength of such a bond. The consequence of causing a pK_a (gas-phase acidity) mismatch between hydrogen bond donor and acceptor was studied via the use of substituent effects for the formic acid–formate anion system (**4**). It was determined that a small difference in pK_a (gas-phase acidities) between the donor and acceptor was not enough to cause a significant decrease in the observed E_{HB}. The dependence of E_{HB} on exact geometry was studied by systematically varying the O—O distance in the formic acid–formate anion complex (**4**) and recalculating the strength of the resulting hydrogen bond. It was found that reasonably small perturbations to the ideal geometry led to fairly significant decreases in the strength of the LBHB. Specifically, a 0.5-Å lengthening of the LBHB between formic acid and formate anion caused a decrease of ca. 6 kcal/mol in its strength. A 1.0-Å lengthening caused a 13-kcal/mol decrease.

These calculations do not suggest that LBHBs are definitely formed during enzyme-catalyzed

processes. However, they do define the parameters which enzymes must ''perfect'' if LBHBs are to play the central role in enzyme catalysis that has been proposed for them.[4–6] These calculations do suggest that the mere existence of polar cavities, or the presence of specific hydrogen-bonding solvent molecules in the enzyme active site, are insufficient reasons to preclude the existence of LBHBs in enzymes, as had previously been suggested.[7–9] Many further studies into these phenomena are currently underway in our laboratory.

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